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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,898	07/14/2003	Rune Robert, Isak, Erik Frants	2183-6260.1US	7453

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
02/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/619,898	FRANTS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 35-41* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 35-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-24-03 & 9-6-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group IV, claims 30-33, 39 and 40, and SEQ ID No. 4 or SEQ ID No. 43 if the selection of a SEQ ID No. requirement is not withdrawn in the reply filed on 9-6-06 is acknowledged. The traversal is on the ground(s) that none of the elected claims recites any particular SEQ ID No and SEQ ID Nos. 1-42 are merely the sequences of 47 exons and flanking sequences of the gene. Upon further consideration of the restricted claims in group IV, the requirement for selecting a single SEQ ID No. has been withdrawn. However, the restriction requirement of group I-VII has been maintained and group IV has been elected for examination.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-29 and 34-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9-6-06.

Applicants' amendment filed 9-6-06 has been entered. Claims 30-33 have been amended. Claim 34 has been canceled. Claim 41 has been added. Claims 1-33 and 35-41 are pending. Claims 30-33 and 39-41 are under consideration.

It is noted that only the subject matter of elected group IV, i.e. an animal or a non-human transgenic animal comprising the claimed nucleic acid molecule, is considered. Amending the claims to commensurate with the subject matter of the elected group IV would be remedial.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in European Patent Office (EPO) 96202707.4 on 9-27-96. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 30 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass human beings having the recombinant expression vector. Human beings are not considered patentable subject mater. See MPEP 2105. This rejection could be overcome by amending the claims to recite "non-human animal" for example.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what are the criteria of the gene to be identified and how to identify said gene.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 30-33 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on chimeric animals and transgenic non-human animal. The claims encompass generation and the use of tens of thousands of numerous different chimeric animals and transgenic non-human animals, such as mice, rats, rabbits, cows, goats, sheep, monkeys, whales, other mammals, birds, fishes, insects etc., comprising a nucleic acid molecule encoding an alpha1 subunit of a P/O-type gated calcium channel or a specific fragment or homolog or derivative of said alhpa1 subunit, or its variants under the control of any promoter or without promoter, and having various unknown and unidentified phenotypes. The specification fails to disclose any chimeric animals or transgenic non-human animal having any particular phenotype. The specification fails to disclose the structural feature or phenotype of the claimed various chimeric animals or transgenic non-human animals. The structural features and phenotypes of the chimeric animals and transgenic non-human animals that can distinguish said chimeric animals and transgenic non-human animals from wild-type animals have not been disclosed. The resulting phenotype of a chimeric animal or a transgenic non-human animal was

unpredictable at the time of the invention (discussed below under enablement rejection section). The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed chimeric animals and transgenic non-human animals, and because the claimed chimeric animals and transgenic non-human animals are highly variant, the information as disclosed in the present application is insufficient to describe the claimed chimeric animals and transgenic non-human animals and their uses.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed chimeric animals and transgenic non-human animals. Thus, it is concluded that the written description requirement is not satisfied for the chimeric animals and transgenic non-human animals and their uses as claimed.

9. Claims 30-33 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of

ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 30-33 and 39-41 are directed to an animal, a non-human animal or a transgenic non-human animal comprising a nuçleic acid molecule encoding an alpha1 subunit of a P/O-type gated calcium channel or a specific fragment or homolog or derivative of said alhpa1 subunit, any gene that comes in contact with said nucleic acid molecule, said nucleic acid molecule that has been modified with or without the control of any promoter, and a non-human animal with phenotype characteristic relating to calcium channel dysfunction and the genome comprises a nucleic acid encoding dysfunctional alpha1 subunit of a P/O-type gated calcium channel

The specification discloses the genomic structure of the human alpha1 subunit of P/O-gated calcium channel gene and localization and identification of the mouse gene related to the neurological mouse mutations tottering, leaning and rolling in the spontaneously aroused mutant mice.

The claims read on chimeric animals and transgenic non-human animal. The claims encompass generation and the use of tens of thousands of numerous different chimeric animals

and transgenic non-human animals, such as mice, rats, rabbits, cows, goats, sheep, monkeys, whales, other mammals, birds, fishes, insects etc., comprising a nucleic acid molecule encoding an alpha1 subunit of a P/O-type gated calcium channel or a specific fragment or homolog or derivative of said alhpa1 subunit, or its variants under the control of any promoter or without promoter, and having various unknown and unidentified phenotypes. The specification fails to disclose any chimeric animals or transgenic non-human animal having any particular phenotype. The specification fails to provide adequate guidance and evidence for what would be the phenotype of the claimed chimeric animals and transgenic non-human animals and how to use those animals.

It is apparent that applicants do NOT have possession of any chimeric animals or transgenic non-human animal, therefore, one skilled in the art at the time of the invention would not know how to use the claimed numerous chimeric animals and transgenic non-human animals. Further, the state of the art of transgenics at the time of the invention held that the phenotype of transgenic animals was unpredictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Wall, R. J., 1996 (Theriogenology, Vol. 45, p. 45-68) states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (e.g. p. 61, last paragraph), and "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies" (e.g. p. 62, first paragraph). In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-

160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that "animal transgenics is still suffering from technical limitations" (e.g. abstract).

Further, the genetic background of the transgenic animal has a large impact on the resulting phenotype of the transgenic animal. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

The resulting phenotype of a transgenic non-human animal comprising a nucleic acid encoding dysfunctional alpha1 subunit of a P/O-gated type calcium channel protein was unpredictable at the time of the invention. Rescher et al., 2004 (Journal of Cell Science, Vol. 117, p. 2631-2639) reports that annexins are unique membrane binding proteins with diverse functions, for example, annexin can be membrane scaffold proteins, involved in

membrane/protein transport, or as an extracellular protein functions as anticoagulant protein, endothelial cell-surface receptor for plasminogen or as anti-inflammatory agent (e.g. abstract, p. 2635, right column, first paragraph). Rescher points out that homozygous annexin A7-/- mice described by Pollard et al., exhibit an embryonic lethal phenotype, whereas annexin A7-/- mice generated by Noegel et al., are viable. Rescher suggests that the difference in the annexin A7-/- mice phenotype could be due to a different genetic background (e.g. p. 2634, left column, first paragraph). Other annexin-knockout mice lacking A1, A2, A5 or A6 do not show obvious phenotype related to a primary defect in vesicle docking and/or fusion event. Rescher reasons that "the annexins targeted in these mice do not serve as essential factors in vesicle docking and/or fusion or that such functions are redundant or taken over by another member of the family during mouse development (e.g. p. 2634, left column, second paragraph).

Mogil et al., 1999 (Pain, Vol. 80, pages 67-82) reports that there are several limitations to the use of mouse transgenic KO models. Mogil teaches that "the embryonic stem (ES) cell lines used to carry the targeted mutation are all derived from various substrains of the 129 strain" and "it is difficult to separate by homologous recombination the 129-derived transgene from tightly linked gene. Even after repeated backcrosses to C57Bl/6, a step most often omitted in the competition to publish, the wild-type and KO populations will differ in their inheritance of so-called "hitchhiking donor gene" alleles". Knockout mutant mice will inherit alleles tightly linked with the gene disruption, leading to "hitchhiking donor gene" alleles from 129 ES cell lines while the wild-type mice will inherit C57BL/6-derived alleles. "[O]bserved phenotypic differences between wild-type and KO mice could, therefore, be due to the targeted mutation, to allelic variation at one or more of the many unidentified hitchhiking genes, or to an interaction

between them" (page 78, left column). In addition, "the background genes from the parent strains can interact with the targeted mutation ("epistasis"), importantly affecting the observed phenotype" (page 78, left column). Leonard et al., 1995 (Immunological Reviews, Vol. 148, pages 97-114) disclosed mice with a disruption in the gc gene that was intended to be a model for X-linked severe combined immunodefkiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, lines 7-9). The claims encompass numerous different transgenic non-human animals and it is apparent that the resulting phenotype of those transgenic non-human animals was unpredictable at the time of the invention in view of the reasons set forth above.

The breadth of claims also encompasses chimeric animal containing cells comprising the claimed nucleic acid molecule. The specification fails to enable making chimeric animals such that they exhibit expression of the claimed nucleic acid molecule. The specification does not correlate chimeric animal, comprising cells with the claimed nucleic acid molecule to any phenotype. The method of making genetic mosaic animal is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Kappel; Sigmund: Mogil) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric animals encompassed by the claims is highly unpredictable. The specification fails to provide the

guidance necessary to overcome this high level of unpredictability to generate a chimeric animal exhibiting any specific phenotype or any phenotype other than wild type. As set forth above, without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art at the time of the invention to determine the use of a chimeric animal comprising the claimed nucleic acid molecule.

Since resulting phenotype of the chimeric animals and transgenic non-human animals expressing the claimed nucleic acid mlecule was unpredictable at the time of the invention, one skilled in the art at the time of the invention would not know whether the claimed chimeric animals and transgenic non-human animals would have any phenotype and whether the phenotype, if any, would be distinguishable from the wild type animals, and would not know how to use the claimed chimeric animals and transgenic non-human animals.

Furthermore, the claims read on using nucleic acid molecule encoding any specific fragment, homolog or derivative of the alpha1 subunit of a P/O-type gated calcium channel protein and numerous structural variants of the alpha1 subunit of a P/O-type gated calcium channel protein. The scope of the claims includes various unknown and unidentified nucleic acids that either encode or not encode a protein.

It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar or higher activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7, IDS) points out that "The significance of particular amino acids and

sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926, IDS) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39, IDS) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. It would be unpredictable for the biological function of any specific fragment, homolog or derivative of the alpha1 subunit of a P/O-type gated calcium channel protein and numerous structural variants of the alpha1 subunit of a P/O-type gated calcium channel protein. Such unpredictability adds to the complexity and unpredictable nature of the claimed chimeric animals and transgenic non-human animal comprising the claimed nucleic acid molecules.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the

level of one of ordinary skill which is high, the amount of the experimentation required and the breadth of the claims that it would require undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER